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ORIGINAL ARTICLE

Prediction of post-operative pancreatic fistula in pancreaticoduodenectomy patients using pre-operative MRI: a pilot study

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Abstract

Background: Post-operative pancreatic fistula (POPF) is one of the most fearful complications which may occur after pancreaticoduodenectomy (PD). The methods used to predict POPF pre-operatively have not been studied in great detail. We analyzed correlation between various parameters related to PD including pre-operative magnetic resonance imaging (MRI) signal intensity (SI), pathology of pancreatic fibrosis and occurrence rates of POPF, and verified that MRI SI results could be the determining values for pre-operative prediction of POPF.

Methods: From January 2005 to August 2006, we retrospectively examined 43 cases of PDs by reviewing abdominal MRI findings, degree of fibrosis of remnant pancreatic stump, and other surgery-related parameters.

Results: POPF encountered in PD were 11 cases (25.6%). Operation time and degree of fibrosis of remnant pancreatic cut surface were related to POPF ($P = 0.030$, $P = 0.010$). The pancreas–liver SI ratio (PLSI) between fistula group and no fistula group was -0.0009 ± 0.2 and -0.1297 ± 0.2, respectively ($P = 0.0004$). The pancreas–spleen SI ratio (PSSI) in each group was 0.423 ± 0.25 and 0.288 ± 0.32, respectively ($P = 0.014$). Using quantitative analysis, the SI ratios were 1.27 and 0.66 in each group ($P = 0.013$).

Conclusions: When analyzing the results of POPF in 43 patients who underwent PD, PLSI, PSSI and qualitative analysis, fistula group differed significantly from no fistula group. Using these results, it will be helpful for us to predict the occurrence of POPF pre-operatively using MRI in PD patients.

Keywords

Post-operative pancreatic fistula, magnetic resonance imaging, pancreaticoduodenectomy

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Introduction

Pancreaticoduodenectomy is now the standard operative procedure for both benign and malignant lesions of the pancreas and periampullary region.[1,2] Besides the difficulties in surgical techniques, post-operative complications of PD are very important. Even although recent advances in surgical techniques and peri-operative management have drastically reduced morbidity and mortality rates after PD, post-operative pancreatic fistula (POPF) remains one of the most fatal complications after PD.[3–12] Several factors predisposing to the development of POPF have been suggested. Old age, a narrow pancreatic duct diameter, soft or normal pancreatic parenchyma, ampullary or duodenal disease, longer operation time, greater intra-operative blood loss and lower surgical volume have been regarded as possible causes of POPF.[3–5,13–25] Even although countless studies were done about POPF, there are no prominent strategies in predicting POPF before it occurs. According to previous reports, magnetic resonance imaging

(MRI) has played an important role in the evaluation of pancreatic parenchyma.[26] At 1.5 T, a T1 weighted image (T1WI) typically shows the pancreas having higher signal intensity (SI) than all the other tissues in the abdomen, including the liver and spleen. Comparing the SI of the pancreas and the liver was enough to differentiate a normal from an abnormal pancreas.[26–30] We postulate that pancreatic parenchymal evaluation with the use of breath-hold unenhanced fat-suppressed T1WI could relate to POPF after PD because of its potential to predict pancreas parenchymal condition. To our knowledge, there is no report regarding the relationship between pre-operative MRI and POPF. In the present study, we retrospectively reviewed various pre-operative parameters of 43 patients who underwent PD and pre-operative MRI. We performed this study to evaluate the accuracy in predicting POPF using of non-enhanced fat-suppressed T1W MRI, and MR data were compared with real pancreatic parenchymal condition.

Materials and methods

Patients

This study was approved by our institutional review board for human investigation. From January 2005 to August 2006, 60 consecutive patients who underwent PD were enrolled in this study. Among the 60 patients, 17 were excluded because they did not undergo MRI ($n = 10$) or they had a MRI at another hospital ($n = 7$). The final study population consisted of 43 patients including 18 (42%) patients with bile duct cancer, 3 (6.8%) patients with pancreatic cancer, 18 (42%) patients with ampullay cancer, 1 (2.3%) patient with chronic pancreatitis, 1 (2.3%) patient with intraductal papillary mucious neoplasm (IPMN), 1 (2.3%) patient with transverse colon cancer and 1 (2.3%) patient with a duodenal gastrointestinal stromal tumor (GIST). All patients underwent pre-operative MRI. The mean interval between MRI and PD was 3.5 days (range of 1–7 days). They included 26 men and 17 women, with an age range of 28–80 years (mean, 61.7 years). The types of PD were: Whipple's operation in 29 patients, pylorus preserving pancreaticoduodenectomy (PPPD) in 13 patients and hepatopancreaticoduodenectomy (HPD) in 1 patient. Since the beginning of the study period, the most relevant patient- and surgery-related data were entered prospectively into a computerized database. For the purpose of this study, we reviewed the medical records, MRI and histopathologic results and analyzed these results retrospectively.

MRI technique and analysis

All MR examinations were performed with 1.5-T superconducting magnets (Sonata; Siemens, Erlangen, Germany) using a torso multicoil array. Breathhold unenhanced fat-suppressed gradient echo (GRE) T1WIs were obtained with a TR of 125 ms, a TE of 2.52 ms, and a flip angle of 70°. The matrix size was 256 × 192. Section thickness was 7 mm for an acquisition time ranging from 28 to 30 s. Fat suppression was used. In quantitative analysis, all SI measurements were performed by one investigator (D.H.C.), who was blinded to the clinical findings and the results of other imaging tests. Standard regions of interests (ROI) were made with an area of 20–45 mm^2. Three SI measurements were obtained in the body and tail of the pancreas which was the residual portion after PD. An average of three measurements was also obtained from the liver and spleen and used as comparison tissue. Pancreas–liver SI ratio (PLSI) and pancreas–spleen signal intensity ratio (PSSI) were calculated as follows: pancreas to comparison tissue SI ratio = [(SI pancreas/SI comparison tissue) − 1]. In qualitative analysis, the examinations were all reviewed on a workstation (Leonardo, Siemens Medical System, Forcheim, Germany). Every examination was analyzed by an experienced radiologist (J.H.K.) who was blinded to the clinical history of the patient and the results of the quantitative analysis. The pancreas SI was qualitatively assessed relative to liver and spleen SI tissue using a five-point scale, as follows: −2 = hypointense compared with the spleen, −1 = same intense as the spleen, 0 = intense between the liver and spleen, 1 = same intense as the liver, 2 = hyperintense compared with the liver (Fig. 1).

Surgical technique and post-operative care

All operations were performed by a team of four surgeons specialized in hepatobiliary and pancreatic surgery. The standard, pylorus-preserving resection involved division of the duodenum 2 cm distal to the pylorus with resection of all of the duodenum distal to the transection site, removal of the gallbladder and common bile duct (proximal to the level of the cystic duct junction), resection of the head, neck and uncinate process of the pancreas and removal of the periampullary lesion. For Whipple's operation, a distal gastrectomy varying from 20% to 40% was performed. In the case of macroscopically suspected margins, frozen sections for these margins were also performed. An end-to-side duct to mucosa type pancreaticojejunostomy was performed. Further downstream, an end-to-side hepaticojejunostomy and side-to-side gastroenterostomy or an end-to-side duodenojejunostomy were made. At the end of the operation, drains were left in the area of the pancreaticojejunostomy and the hepaticojejunostomy. All patients were managed according to a standard post-operative pathway. All patients received H2 blocker during the entire post-operative hospital course, and octreotide treatment was continued for 7 days after the operation. We checked the fluid volume and amylase concentration from drains on post-operative days 1, 3, 5, 7, and 10.

For the definition of POPF, we made reference to the International Study Group on pancreatic fistula.[3,31]

We defined POPF using a combination of the following: drainage of more than 50 ml of fluid with amylase content greater than three times the upper normal serum value using surgically placed drains on post-operative day 10, or pancreatic anastomotic disruption demonstrated by a radiograph, with or without the presence of patient's clinical symptoms [peritoneal tenderness, progressive abdominal pain, body temperature > 38.5°C, leukocytosis (white blood cell > 15 000/l)].

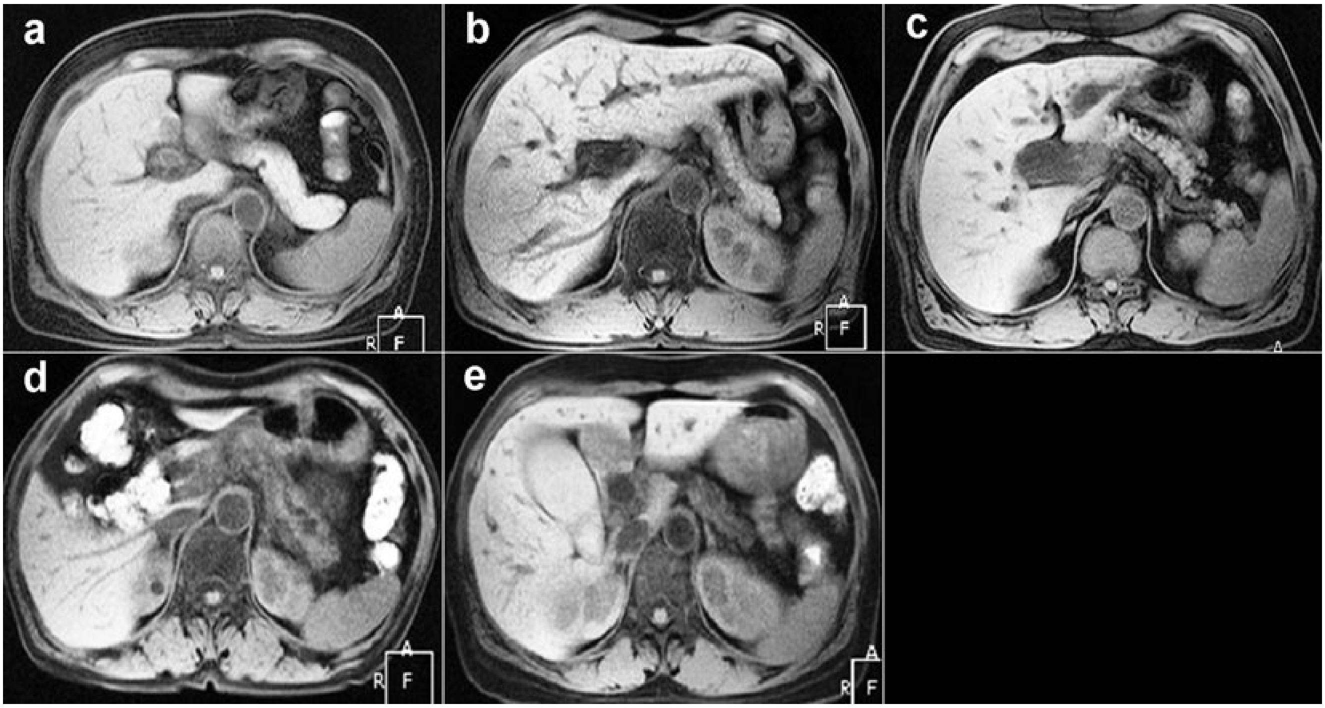

Figure 1 Pancreas grading in the pre-operative fat suppressed MRT1WI. Pancreatic signal intensity (SI) was qualitatively assessed relative to the liver and spleen SI using a five-point scale. When the pancreas SI was higher than the liver, it was defined as Grade 2, Grade 1 was defined as a SI of the pancreas and spleen. When the pancreas SI was between the liver and spleen, it was defined as Grade 0, Grade –1 means a pancreatic SI equal to the spleen, and in Grade –2 pancreas SI was lower than the spleen. (a) Grade 2, (b) Grade 1, (c) Grade 0, (d) Grade –1, (e) Grade –2

Pathologic analysis (assessment of fibrosis in pancreatic stump)

The tissues of the pancreatic stump obtained during surgery were fixed in formalin, dehydrated and embedded in paraffin. The pancreatic tissues that indicated a mirror image of the pancreatic stump anastomosed with jejunum were post-operatively processed with hematoxylin and eosin (H&E) and Masson's trichrome staining for accurate estimation of the degree of fibrosis. Every examination was analyzed by an experienced pathologist (S.Y.J) who was blinded to the clinical history or radiologic results of any of the patients. The degree of fibrosis was categorized by intralobular fibrosis and interlobular fibrosis compared with the normal pancreas. Each type was assessed by the criteria of Klopper and Maillet[32] into two categories: weak, i.e. fibrosis of degree 0 to 3 and heavy, i.e. degree 4 to 6. The sum of degrees of each fibrous type represented the grade of fibrosis in the pancreatic stump of each patient (Fig. 2).

The degree of fatty infiltration in the parenchyma of the pancreatic stump was estimated as 0 (absent), 1 (mild, 1–5%), 2 (moderate, 6–20%) and 3 (marked, >20%).

Statistical analysis

Statistical analysis was performed using the SPSS software (SPSS v. 12.0; SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using the unpaired, independent, two-tailed *t*-test. Continuous data are reported as the mean ± standard deviation. The χ^2-square test was used for univariate analysis of categorical data. Receiver-operating characteristic (ROC) curves were constructed to establish the optimal cut-off value of MR parameters in predicting POPF. Sensitivity and specificity were calculated in accordance with standard methods. A *P*-value of less than 0.05 was considered statistically significant.

Results

Among the 43 patients who underwent PD, POPF was present in 11 patients (25.6%). The demographics and general characteristics are summarized in Table 1. In the pre-operative period, serologic test, liver function tests and total bilirubins were abnormal, and tumor markers were also elevated, but, in general, no laboratory test proved to be related to POPF. Table 2 shows parameters related to operation between the fistula and no fistula group. The type of operation, amount of blood loss, hospital days and pancreatic duct size showed no significant relationship to POPF. Among these parameters we investigated, only the operation time was related to POPF ($P = 0.030$). Table 3 showed MR parameters between the fistula group and no fistula group. In the PLSI ratio using MRI, the value of the PLSI ratio in patients in the fistula

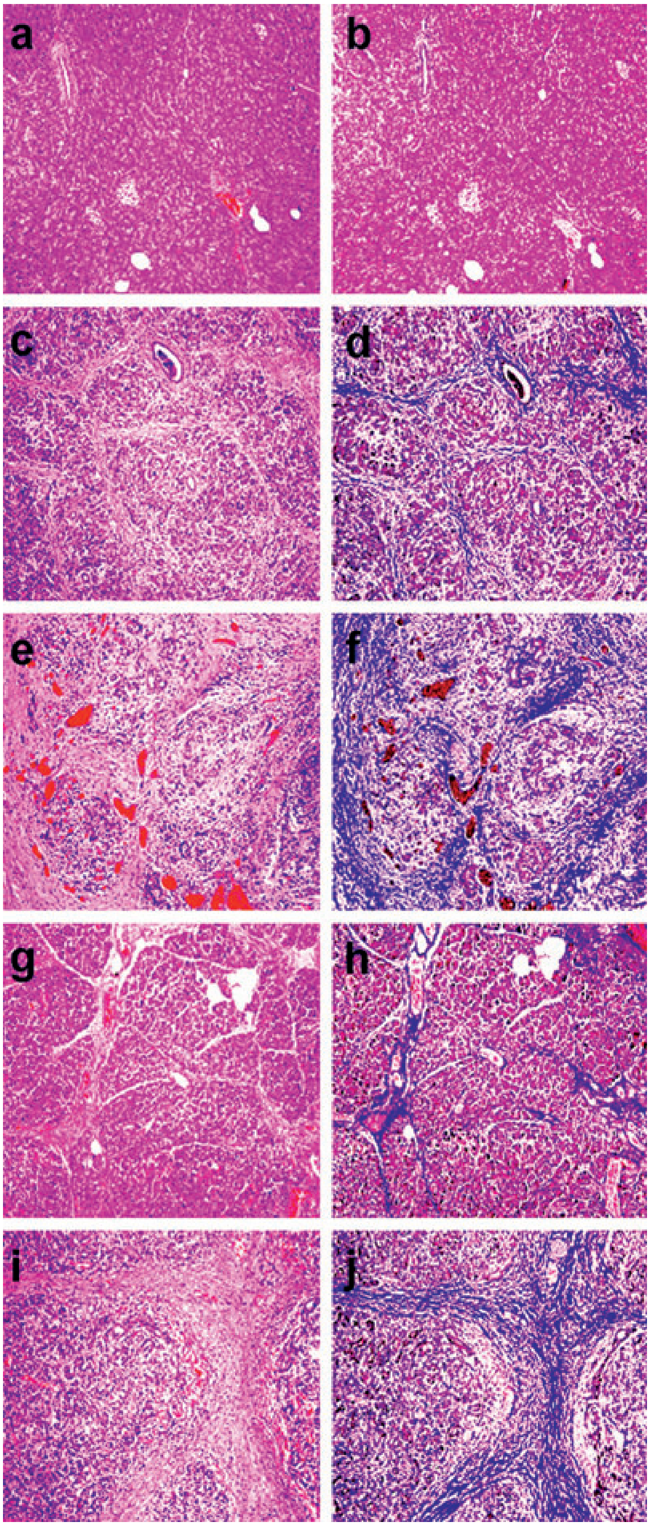

Figure 2 Hematoxylin and eosin (H&E) staining and Masson's Trichrome staining of the normal pancreas. (a) H&E stain, (b) Masson's Trichrome stain. Fibrosis grading of the pancreas. Pancreatic fibrosis was graded from 0 (none) to 6 (severe) according to the severity of fibrosis, and was divided into intralobular fibrosis and interlobular fibrosis. The sum of each scoring was from grade 0 to grade 12. (c) Mild intralobular fibrosis in H&E stain, (d) mild intralobular fibrosis in Masson's stain, (e) severe intralobular fibrosis in H&E stain, (f) severe intralobular fibrosis in Masson's stain, (g) mild interlobular fibrosis in H&E stain, (h) mild interlobular fibrosis in Masson's stain, (i) severe interlobular fibrosis in H&E stain and (j) severe interlobular fibrosis in Masson's stain (Original magnification a–j: ×100)

Table 1 Demographics and general considerations of the patients

	Fistula $n = 11$	No fistula $n = 32$	*P* value
Gender			
Male	5 (45.5)[a]	21 (65.6)	NS
Female	6 (54.5)	11 (34.4)	
Mean age (years)	61.9	61.5	NS
Pathology			
Pancreatic cancer	0 (0)	3 (9.4)	NS
Bile duct cancer	6 (54.5)	12 (37.6)	NS
Ampullary cancer	5 (45.5)	13 (40.6)	NS
IPMN	0 (0)	1 (3.1)	NS
Chronic pancreatitis	0 (0)	1 (3.1)	NS
Transverse colon cancer	0 (0)	1 (3.1)	NS
Duodenal GIST	0 (0)	1 (3.1)	NS
Laboratory values			
Mean hemoglobin (g/dl)	12.1	12.1	NS
Mean albumin (g/dl)	3.7	3.6	NS
Mean BUN (mg/dl)	13.2	14.0	NS
Mean creatinine (mg/dl)	0.7	0.7	NS
Mean AST (U/l)	104.2	124.3	NS
Mean ALT (U/l)	152.3	174.8	NS
Mean LDH (U/l)	412.8	436.3	NS
Mean total bilirubin (mg/dl)	4.5	7.4	NS
Mean CA19-9 (U/ml)	601.7	342.8	NS

[a]Values in parentheses are percentages

group was –0.1297 ± 0.2, whereas the value of the PLSI ratio in patients in the no fistula group was –0.0009 ± 0.2 ($P = 0.0004$). In the PSSI ratio using MRI, the value of the PSSI ratio in patients in the fistula group was 0.423 ± 0.25, whereas the value of the PSSI ratio in patients in the no fistula group was 0.288 ± 0.32 ($P = 0.014$). In qualitative analysis using MRI, the score in patients within the fistula group was –1.27, whereas the score in patients within the no fistula group was 0.66 ($P = 0.013$). In mean pancreas fibrosis using pathology, the score in patients within the fistula group was 2.36 ± 1.36, whereas the score in patients within the no fistula group was 4.56 ± 3.98 (P = 0.010). Figure 3 shows diagnostic performance for preoperative predictions of POPF with each MR parameter. The diagnostic performance for preoperative predictions of POPF was better with the qualitative analysis (Az = 0.653) than with the PLSI ratio (Az = 0.640) and PSSI ratio (Az = 0.613); although, there was no statistically significant difference in each MR parameter. The optimal cut-off value between fistula group and no fistula group on each MR parameters was −0.12097 in the PLSI ratio (sensitivity = 36%, specificity = 89%), 0.29979 in the PSLSI ratio (sensitivity = 79%, specificity = 45%) and 0.5 in qualitative analysis (sensitivity = 91%, specificity = 34%) using the ROC curve.

Table 2 Parameters related to operation

	Fistula n = 11	No fistula n = 32	P-value
Name of operation			
Whipple's operation	6 (54.5)[a]	23 (68.8)	NS
PPPD	5 (45.5)	8 (25.1)	NS
HPD	0 (0)	1 (3.1)	NS
Other operative parameters			
Mean operation time (min)	492.0	565.2	0.030
Mean blood loss (ml)	960.0	1037.5	NS
Mean hospital days	26.3	36.9	NS
Mean P-duct size (mm)	3.5	4.6	NS
Mean CBD size (mm)	14.4	14.0	NS

[a]Values in parentheses are percentages

Discussion

POPF is still the 'Achilles heel' of the PD. Even at tertiary care hepatobiliary centers, leakage rates at the pancreaticojejunostomy are over 10%. A wealth of surgical literature has been devoted to various technical aspects of PD. Before the 1980s, mortality rates of 20% were common, and morbidity rates were even higher. The most frequent source of major morbidity after PD is leakage at the site of pancreatic anastomosis: this most often results in peri-pancreatic fluid collection, abscess, development of a pancreatic fistula or bleeding from adjacent major vessels. Countless methods have been described to reduce POPF rates, including descriptions of various anastomotic techniques, the use of external stenting for the pancreatic duct, reinforcement of anastomosis with fibrin glue or with round ligament, using the surgical microscope and occluding of the pancreatic duct.[11,23–25,33–38] What is clear from the literature is that numerous techniques may be associated with low rates of POPF and that the occurrence of POPF reliably relates to several predominant factors. The texture of the pancreas and size of the pancreatic duct seem to be major risk factors for

Table 3 Correlation between post-operative pancreatic fistula (POPF) and signal intensity (SI) ratio by fat suppressed MRT1WI compared with pancreatic fibrosis grade

	Fistula	No fistula	P-value
Pancreas–liver SI ratio (PLSI)	−0.0009 ± 0.2	−0.1297 ± 0.2	0.0004
Pancreas–spleen SI ratio (PSSI)	0.423 ± 0.25	0.288 ± 0.32	0.014
Qualitative analysis	1.27	0.66	0.013
Mean pancreas fibrosis (grade)	2.36 ± 1.36	4.56 ± 3.98	0.010

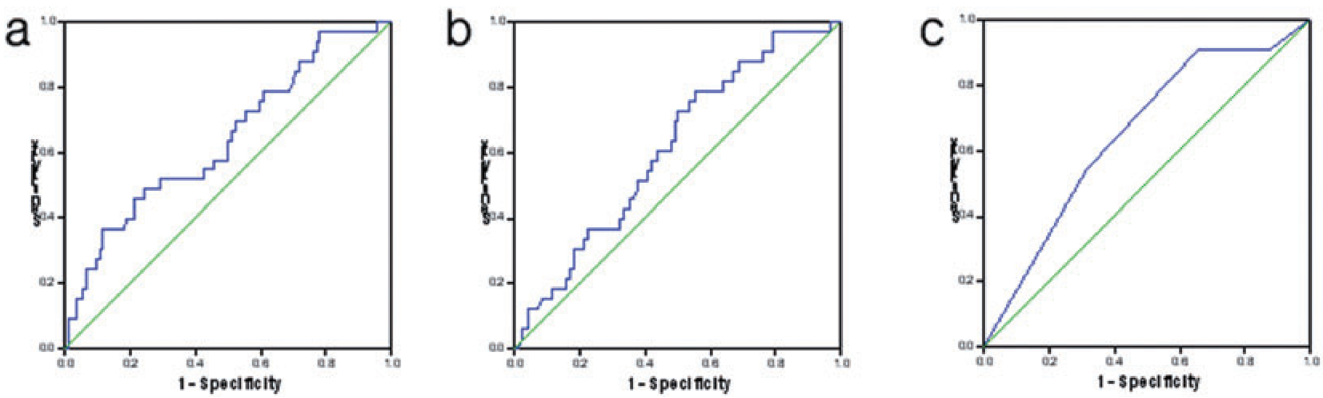

Figure 3 The diagnostic performance for the pre-operative predictions of post-operative pancreatic fistula (POPF). The Az values (area under the ROC curve) of the PLSI ratio, PSSI ratio and qualitative analysis were 0.640 (95% CI: 0.529–0.751), 0.613 (95% CI: 0.507–0.719) and 0.653 (95% CI: 0.548–0.759), respectively. (a) Receiver operating characteristics (ROC) curve of the PLSI, (b) ROC curve of the PSSI and (c) ROC curve of the qualitative analysis

POPF. A small pancreatic duct and soft pancreatic texture are consistently associated with higher POPF rates, presumably because smaller ducts make the anastomosis inherently more technically challenging. When the pancreas is soft and fragile, even an atraumatic needle causes a small leakage of pancreatic juice. It is also likely that a more normal pancreas has a higher output of pancreatic enzymes. However, these parameters which are related to a pancreatic fistula can usually be determined during surgery or the post-operative period. No studies have shown the prediction of a pancreatic fistula pre-operatively. If only it becomes predictable, it will be very helpful for surgeons pre-operatively. More care will be taken when operating on the so-called 'high-risk group'. In the present study, the focus was on finding out the predictive factors for POPF using MR parameters compared with fibrosis of the pancreas stump.

Recently, pre-operative MRI has been adapted as a routine diagnostic tool for periampullary lesions as a result of its non-invasiveness and a lot of diagnostic information. MRI has also played an important role in the evaluation of pancreatic parenchyma. Fat-suppressed techniques are now available to decrease chemical shift, truncation and breathing artifacts and to improve dynamic range. Good quality breathhold sequences and increased spatial resolution can be obtained using the torso multicoil array. The normal pancreas shows hyperintense relative to all other solid abdominal tissues on T1WI in multiple studies. In abnormal pancreatic parenchyma, the pancreatic parenchymal SI decreased. This is caused by pancreatic atrophy, fibrosis, edema and fat infiltration.[26,27,30] Breathhold unenhanced fat-suppressed T1WI offers excellent potential for depicting POPF.[26–30] In our study, MR parameters including PLSI, PSSI and qualitative analysis showed significant relationships with pancreatic fistula. These MR parameters can predict pancreatic fistula before PD. Even although there was no statistical significance, the qualitative analysis showed the best performance. So we can apply these methods in predicting the possibility of POPF pre-operatively.

Most studies described that a soft pancreas caused more POPF than a hard pancreas. In our study, pancreatic fibrosis grading assessed using the criteria of Klopper and Maillet[32] was related to POPF. Furthermore, fat content in the pancreatic stump was not related to POPF (data not shown), indicating that pancreatic fibrosis is closely related to POPF which was mentioned in pervious reports in the literature.

There were some limitations to this study. First, even although we showed potent possible relationships between POPF and various MR SI ratios, we still do not have perfect methods to prevent a pancreatic fistula after PD. However, recently, several brand new surgical techniques using omental flap or round ligament of the liver for pancreaticojejunostomy protection have been reported.[11,15,23–25,33–38] These techniques could be applied to so-called 'high-risk patients' in terms of MRI PLSI, PSSI and qualitative analysis of pancreas parenchyma. Second, the case number was relatively small and study was designed retrospectively. Therefore, a prospective large-scale study should be done. Third, the pancreatic fibrosis index which was calculated in the pancreatic stump tissue could not represent the whole pancreas.

In conclusion, the MRI PLSI, PSSI and qualitative analysis of pancreas parenchyma were definitely related to POPF after PDs. Using this result it will be helpful for us to predict the occurrence of a pancreatic fistula pre-operatively in the future and to reduce pancreatic fistula-related complications.

Conflicts of interest

None declared.

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